Potential of Breath Analysis: From Environmental Exposure Assessment to Medical Diagnosis

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Abstract

Exhaled breath analysis is becoming one of the desirable strategies for environmental exposure assessment as well as for clinical diagnosis because it provides a relatively inexpensive, rapid, and noninvasive monitoring method. The presence of specific compounds in a human breath can indicate a recent exposure to pollutants or a disease state of the individual. Breath analysis has attracted a considerable amount of scientific and clinical interest over the past decade. This review describes the potential applications of human breath analysis, including monitoring of environmental exposure to pollutants and clinical diagnosis of diseases, with particular attention to exogenous volatile compounds and endogenous volatile biomarkers.

Introduction

Sampling and analysis of exhaled breath is preferred to direct measurement of analytes from blood samples because breath collection is easier to perform, potentially inexpensive, faster, totally painless, and agreeable to people [1,2]. Breath matrix is less complex than blood and other body fluids. Breath is noninvasively available and continuously accessible. Since human is constantly inhaling air from its environment as he breathes in the ambient air, exhaled breath may reflect the environmental exposure of an individual to pollutants. An example of area which is based on this principle is the field of inhalation toxicology, where the environmental exposure of personnel to volatile and semi-volatile compounds is readily assessed by measuring their concentrations or their metabolites in the exhaled breath.

Another area of interest in medicine is breath test for clinical diagnosis. Volatile organic compounds (VOCs) endogenously produced in human exhaled breath are representative of blood-borne concentrations via gas exchange between the blood and the alveolar air in the lungs. Therefore, the presence of specific VOCs in exhaled breath can be an indicator of a biological response of the subject and their monitoring could conceivably replace a direct blood measurement. In recent years, interest in analysis of breath endogenous volatile biomarkers for diagnostic purposes has increased.

Thus, depending on the exogenous or endogenous origin of the VOCs in human exhaled breath, the typical applications of breath analysis fall into the category of exposure assessment to environmental pollutants or the category of clinical diagnosis of disease. The purpose of this paper is to review the breath analysis aspects of exposure assessment and clinical diagnosis, with emphasis on exogenous volatile compounds and endogenous volatile biomarkers.

Breath Analysis and Assessment of Exposure to toxic VOCs

Ambient-air VOCs enter the body mainly through inhalation and transfer to the blood at the alveoli, where they reach equilibrium with the arterial blood. At the equilibrium, the relative concentration of each VOC in the interface between the blood and the alveolar breath is determined by its partition coefficient. A reasonable estimate of the partition coefficient allows estimation of the VOC concentration in the arterial blood from the breath measurement. Knowing the blood concentration then allows estimation of concentrations in other body tissues by using a model of the target VOC distribution in the body.

Several works illustrated the utility of monitoring VOCs in exhaled breath to supplement field exposure studies. In the so called Total Exposure Assessment Methodology (TEAM) studies, the United States Environmental Protection Agency broadly applied spot breath measures to monitor the distribution of common VOCs, semi-VOCs, and particulate matters and to compare individual body burden to environmental levels [3,4]. Brugnone et al. [5] demonstrated that the measurement of benzene, toluene, cumene, and styrene in the breath can be successfully used to assess non-occupational exposures. Jo et al. [6] used chloroform breath tests to assess exposures to chlorinated tap water from showering. Using breath analysis, Aggazzotti et al. [7,8] investigated exposures...
to a series of chlorinated disinfection by-products from swimming pools. Pleil et al. [9] measured alkanes and aromatics in breath to assess total exposures at Air Force bases for workers to military jet fuel constituents. Schreiber et al. [10] used breath test to assess exposures to tetrachloroethylene in subjects living above a dry cleaning establishment. All these studies showed that VOC measurements in exhaled breath are significantly correlated to blood and/or ambient air concentrations.

Breath Analysis and Assessment of Exposure to Pneumotoxic Metals

The lung represents also the main route of entry of most particulate matters into the body. Aerosols with size less than 10 µm are readily in- and exhaled via the lungs. In one day, the average person in- and exhales 8640 L of air and expires almost 500 mL of water. This means that the amount of the poorly-soluble metallic species which are expired every day by a human could be substantial. According to Corradi and Mutti, it may represent about 20% of total daily excretion for several elements [11]. Therefore, the elemental analysis of exhaled breath may be used for monitoring of target tissue levels of inhaled metallic elements.

In a related study, Goldoni et al. [12] collected and analyzed urinary samples and exhaled breath condensate (a fluid obtained by cooling exhaled air) from workers exposed to cobalt (Co) and tungsten (W) and from nonexposed workers. Data distribution indicated that the concentrations of Co and W were higher in breath from exposed workers as compared to nonexposed workers. Both Co and W in the breath of exposed workers were higher at the end of the work shift in comparison with preexposure values. Moreover, Co and W levels in the breath were positively correlated with respective urinary concentrations. Authors concluded that their results suggest the potential usefulness of exhaled breath to complete and integrate biomonitoring and health surveillance procedures among workers exposed to pneumotoxic metals. Caglieri et al. [13] carried out a similar study on workers exposed to chromium Cr(VI) and found that Cr(VI) levels in exhaled breath condensate were higher in exposed workers than nonexposed controls, and they were positively correlated with both urinary and ambient air Cr(VI) levels.

Breath Analysis and Clinical Diagnosis of Disease

Human breath primarily is comprised of nitrogen, oxygen, carbon dioxide, water vapor, and inert gases. The detection of VOCs in exhaled breath for diagnostic purposes has a long history. Ancient Greek physicians already used odor from a patient breath for assessing clues to diagnosis. In 1971, Pauling et al. [14] identified more than 250 compounds in the human breath. Since this and other early studies, the prospects for using breath biomarkers for the early detection of complex diseases have been increasingly explored. Now, it is known that more than 3,000 different compounds can be detected in exhaled air, of which only 20–30 are present in all subjects. Their amount may change depending on gender, age, life style, and health state. In disease states of the organism, concentrations of some VOCs change and/or some additional compounds are produced [15]. Several studies have demonstrated that breath analysis is a potential screening tool for the early detection of complex diseases.

The principle behind the science of breath analysis is based on cell biology. Pathophysiological processes produce inside the human body endogenous VOCs which are transported via the bloodstream, diffuse from the blood into the breath via permeation across the alveolar membrane, and are exhaled through the lungs as breath volatiles [16,17]. This is due to an almost instantaneous equilibrium between pulmonary blood and air in the lung alveoli. Endogenously produced VOCs are excreted in the lung alveolar air within minutes of the formation because of their low solubility in the blood. Breath serves as a shortcut for endogenous metabolites to come out of the body. Exhaled breath VOCs reflect the internal bodily conditions and therefore, can be considered as disease biomarkers. As changes in the blood chemistry lead to measurable changes in the breath, metabolic changes in a human body can practically be monitored in vivo via collection and analysis of alveolar breath [18,19]. Quantitative compositional analysis of exhaled breath may thus provide an attractive noninvasive diagnostic strategy for complex diseases.

So far, several breath VOCs are recognized as disease biomarkers. Increase levels of acetone in breath accompany uncontrolled diabetes [20]. According to Phillips et al. [21], acetone is also a potential biomarker of lung cancer. Formaldehyde
increases in breath from patients with bladder or prostate cancer [20]. Ethane and pentane are supposed to be characteristic of breast cancer, bronchial asthma and rheumatoid arthritis [22-24]. Concentration of isoprene has been found higher in breath of patients with lung cancer or hypercholesterolemia than in control groups [25,26]. Dimethylsulfide is characteristic of exhaled breath from cirrhotic patients, while dimethylamine and trimethylamine are elevated in patients suffering from renal failure [20]. Heptanal and hexanal are recognized to be characteristic of patients with breast or lung cancer [21,27]. Benzene, toluene, ethylbenzene and xylene isomers are proposed as lung cancer biomarkers [27,28]. The list is by no means exhaustive. The origin pathway of only few breath VOCs is known. For example, ethane and pentane are formed during lipid peroxidation of fatty acid components of cell membranes, triggered by reactive oxygen species. Acetone is produced by decarboxylation of acetoacetate which derives from lipid peroxidation [2,28].

As a result of extensive studies, some breath biomarkers have been discovered and successfully used in diagnosis of disease or other applications. However, only a few breath tests have been standardized and approved because of a lack of validated diagnostic procedure. Nitric oxide test is used for asthma, carbon monoxide test for neonatal jaundice, $^{13}$CO$_2$ test for Helicobacter pylori infection, branched chain hydrocarbons for monitoring of heart transplant rejection, hydrogen test for carbohydrate metabolism, and ethanol test for law enforcement [1].

**Conclusion**

This short review forcefully indicates that the noninvasive breath analysis in both environmental exposure assessment and clinical diagnosis may provide a promising alternative strategy in that it can be performed repeatedly and without limits to amount (unlike blood), timing (unlike urine), or frequency (unlike radiography). Several studies reported a number of very promising results revealing interesting properties of various VOCs for exposure assessment and clinical diagnosis. Exhaled breath analysis has the potential to be inexpensive, portable, and offers the possibility of providing real-time results in workplace, point-of-care or at-home testing. Disadvantages of breath testing include the multitude of possible confounders and the lack of standardization of procedures for sampling, analysis and background correction.

**References**

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